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Differential susceptibility in youth: evidence that 5-HTTLPR x positive parenting is associated with positive affect ‘for better and worse’

BL Hankin¹, E Nederhof², CW Oppenheimer¹, J Jenness¹, JF Young³, JRZ Abela³, A Smolen⁴, J Ormel² and AJ Oldehinkel²

Positive affect has been implicated in the phenomenological experience of various psychiatric disorders, vulnerability to develop psychopathology and overall socio-emotional functioning. However, developmental influences that may contribute to positive affect have been understudied. Here, we studied youths’ 5-HTTLPR genotype and rearing environment (degree of positive and supportive parenting) to investigate the differential susceptibility hypothesis (DSH) that youth carrying short alleles of 5-HTTLPR would be more influenced and responsive to supportive and unsupportive parenting, and would exhibit higher and lower positive affect, respectively. Three independent studies tested this gene–environment interaction (GxE) in children and adolescents (age range 9–15 years; total $N = 1874$). In study 1 ($N = 307$; 54% girls), positive/supportive parenting was assessed via parent report, in study 2 ($N = 197$; 58% girls) via coded observations of parent–child interactions in the laboratory and in study 3 ($N = 1370$; 53% girls) via self report. Results from all the three studies showed that youth homozygous for the functional short allele of 5-HTTLPR were more responsive to parenting as environmental context in a ‘for better and worse’ manner. Specifically, the genetically susceptible youth (that is, S’S’ group) who experienced unsupportive, non-positive parenting exhibited low levels of positive affect, whereas higher levels of positive affect were reported by genetically susceptible youth under supportive and positive parenting conditions. These GxE findings are consistent with the DSH and may inform etiological models and interventions in developmental psychopathology focused on positive emotion, parenting and genetic susceptibility.

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Introduction

Extensive research in affective neuroscience has demonstrated the importance of positive emotion for protecting against psychiatric disorders and building resiliency and healthy development.^{1–4} Low levels of positive affect have been directly implicated in risk to depression,^{5–10} and dysregulation in emotion regulation, especially difficulty in upregulating positive emotion, has been implicated in several psychiatric disorders.^{11–13} Given the significant role of positive affect in the promotion of adaptive and healthy social-emotional functioning, it is important to advance knowledge about factors that contribute to positive emotion in children and adolescents.

Parenting is one well-studied factor affecting youths’ level of positive affect. Children and adolescents who experience warm, sensitive, supportive and positive parenting have been shown to exhibit higher levels of positive affect, demonstrate better social-emotional functioning and are at a reduced risk for the development of psychopathology.^{14–17} Moreover, recent research on gene–environment interactions (GxE) underscores individual differences in how youth are influenced by their parents’ behaviors.^{18–22}

The present work examined a novel, specific and *a priori* GxE that was hypothesized to affect youths’ level of positive

affect based on the differential susceptibility hypothesis (DSH).^{23–26} The majority of prior GxE research has been guided implicitly by a vulnerability–stress framework.^{27,28} This traditional vulnerability perspective highlights that certain individuals, frequently for genetic reasons, are more vulnerable to psychopathology and poor outcomes compared with others, and this risk is exerted only in response to the negative effects of environmental influences. In contrast, the DSH proposes that some individuals, often for genetic reasons, are more responsive to environmental experiences in a ‘for better and worse’ fashion.²⁹ These genetically susceptible individuals are expected to exhibit poor functioning and psychopathology under adverse environmental conditions (for example, negative events), but also to flourish and benefit from the positive environmental conditions (for example, supportive parenting).

The DSH is a relatively new conceptual model, therefore there is little research to date explicitly and fully testing its proposals. Recent reviews of the GxE findings that pertain to some aspects of the model find evidence consistent with the view that genetically susceptible individuals react to stressful environmental contexts with negative outcomes, and with positive outcomes under supportive environmental

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conditions.^{25,30} However, the vast majority of extant studies have investigated GxE effects that focus on the absence of negative environments (for example, no maltreatment) and lack of negative outcomes (for example, no depression). Essential for investigating DSH's central hypothesis that genetically susceptible individuals respond to environmental context in a 'for better and worse' manner is an assessment of positive/supportive environments, not merely the absence of negative environmental conditions. Moreover, to fully investigate differential responses to a range of environments, it is critical to assess positive, competent functioning and not solely the absence of negative outcomes. Indeed, in their recent review, Belsky and Pluess²⁵ noted only one study³¹ that explicitly evaluated whether genetically susceptible individuals (adults with allelic variation in 5-HTTLPR) reacted to the environmental contexts (early family risk) in a 'for better and worse' fashion. Taylor *et al.*³¹ found both increased risk for negative outcomes under adverse conditions, as well as enriched outcomes under supportive conditions.

In summary, the present study sought to advance knowledge on GxE effects that are hypothesized to contribute to youths' positive affect. As scant research has investigated whether genetically susceptible individuals flourish in response to supportive environments,³¹ and no study has investigated this hypothesis with youth, we sought to explicitly examine whether genetically susceptible youth, specifically 5-HTTLPR short-allele carriers, would exhibit both low and high levels of positive affect under the environmental contexts of the lack of positive parenting to supportive parenting, respectively.

We elected to study allelic variation in 5-HTTLPR, a polymorphism in the serotonin transporter promoter gene area (SLC6A4), because Taylor *et al.*³¹ examined 5-HTTLPR in the only study showing full differential susceptibility. Also, considerable prior GxE research has investigated adverse environmental influences interacting with the 5-HTTLPR for many psychiatric outcomes.^{32–35} We chose to assess parenting behavior, specifically the range from non-supportive to positive/supportive parenting, as the environmental context given extensive research documenting associations with youths' positive affect and overall social-emotional functioning.^{14,15}

Here, we report evidence from three independent studies demonstrating the *a priori* hypothesized GxE predicting youths' positive affect, consistent with the DSH's 'for better and worse' conceptualization. In the first study, parents reported on the degree to which they use positive/supporting parenting. In the second study, parenting behaviors were observed in the laboratory. In the third study, positive parenting was operationalized as the emotional warmth perceived by the youth themselves. Positive affect was assessed using varying self reported questionnaires. Given well-known and publicized lack of replication in GxE research,^{33,36} we tested this GxE hypothesis in three independent samples using multiple methods to assess environment input (that is, parenting) and positive affect. This consistent finding across the three studies suggests a robust effect that youth homozygous for the short allele of 5-HTTLPR exhibit differential susceptibility to experience positive affect as a function of parental positivity and support.

Materials and methods

Study 1

Participants and procedures. Participants were 307 youth (54% girls; 31% 3rd grade, 35% 6th grade, 34% 9th grade; 67% White; 7% African–American; 7% Latino; 4% Asian; 15% mixed ethnicity) recruited from public schools. The youth came to the laboratory with a parent (85% mothers). After the parent completed an informed consent form and the youth completed an assent form, the youth provided a DNA sample and they both completed a battery of questionnaires.

Measures. Parents completed the positive parenting subscale of the Alabama Parenting Questionnaire.³⁷ The positive parenting scale consists of six items. It is a frequently used, reliable and valid measure of positive parenting.^{38,39} Youth completed the positive affect subscale from the Positive Affect and Negative Affect Scale for Children,⁴⁰ which is a frequently used, reliable and valid measure of youths' positive affect levels.⁴¹

Genotyping. Children provided buccal cells for DNA collection via Oragene kits from DNA Genotek (Ottawa, ON, Canada). Genomic DNA was collected and isolated using standard salting out and solvent precipitation methods. The 5-HTTLPR alleles were assayed⁴² and modified by using primers reported by Hu *et al.*⁴³ The rs25531 single-nucleotide polymorphism genotypes (LA vs LG) were obtained by incubating the PCR products with MspI.⁴⁴ Samples were analyzed on an ABI PRISM 3130xl Sequencer (Carlsbad, CA, USA). Three groups of participants were formed based on their genotyping: children homozygous for the higher expressing LA allele (L'L'), children heterozygous for the lower expressing alleles (S'S') and those heterozygous (L'S'). The 5-HTTLPR polymorphisms were in Hardy–Weinberg equilibrium. Genotype frequencies were 20 L'L', 47 L'S' and 32% S'S'. Genotype frequencies did not vary significantly by race ($\chi^2 = 1.42$, $P = 0.23$) or sex ($\chi^2 = 0.67$, $P = 0.41$).

Study 2

Participants and procedures. Participants were 197 youth (58% girls; 27% 3rd grade, 35% 6th grade, 38% 9th grade; 64% White; 6% African–American; 10% Latino; 4% Asian; 15% mixed ethnicity) recruited from public schools. The youth came to the laboratory with a parent (80% mothers). After the parent completed an informed consent form and the youth completed an assent form, the youth provided a DNA sample and together they were observed during a parent–child discussion.

Youth completed the Positive Affect and Negative Affect Scale for Children and provided a DNA sample, which was genotyped with exactly the same procedures as study 1. The 5-HTTLPR polymorphisms were in the Hardy–Weinberg equilibrium. Genotype frequencies were 20 L'L', 53 L'S' and 27% S'S'. Genotype frequencies did not vary significantly by race ($\chi^2 = 0.001$, $P = 0.98$) or sex ($\chi^2 = 1.56$, $P = 0.21$).

Parenting behaviors were ascertained during videotaped observations of parent–child interactions in the laboratory. Behaviors were coded on a 1–5 scale (1: poor/unsupportive–5: positive/supportive parenting), specifically for positive regard

and support by a trained team of reliable coders (intraclass correlation (ICC) = 0.71). Such parent–child interaction tasks and coding have been used previously and shown good reliability and validity.^{5,45}

Study 3

Participants and procedures. Participants ($N=1370$, 53% girls and 86% from the Dutch ancestry) came from the Dutch prospective cohort study TRAILS.^{46,47} Data from the first, second and third wave were used, at ages 11.09 (s.d. = 0.59), 13.55 (s.d. = 0.54) and 16.13 (s.d. = 0.59), respectively. All procedures have been approved by the Central Committee on Research Involving Human Subjects. Both participants and their parent signed informed consent before participation. The participants filled out questionnaires at school, under the supervision of TRAILS assistants.

Measures. Perceived positive parenting was assessed at the first wave, by the 18-item Emotional Warmth scale of the EMBU (a Swedish acronym for My Memories of Upbringing) for children (EMBU-C),⁴⁸ which has very good psychometric properties.^{49,50} The answers for both the parents were highly correlated ($r=0.79$), and therefore combined into a single measure. Positive affect was measured at the second wave, by the Behavioral Activation System Drive scale of the Behavioral Inhibition System/Behavioral Activation System scales.⁵¹ This scale was selected because it has good psychometric properties and showed the highest correlation with positive affect as assessed with the Positive Affect and Negative Affect Scale.^{51,52}

Genotyping. DNA was extracted from blood samples or buccal swabs using a manual salting procedure.⁵³ The length of the 5-HTTLPR alleles was determined by direct analysis on an automated capillary sequencer (ABI3730, Applied Biosystems, Nieuwerkerk a/d IJssel, The Netherlands). The rs25531 single-nucleotide polymorphism genotypes (LA vs LG) were obtained using a custom-made Taqman assay (Applied Biosystems). For more details see Nederhof *et al.*⁵⁴ The 5-HTTLPR polymorphisms were in Hardy–Weinberg equilibrium. Genotype frequencies were 24 L'L', 50 L'S' and 26% S'S'. Genotype frequencies did not vary significantly by sex ($\chi^2=1.07$, $P=0.59$) or ethnicity ($F=1.35$, $P=0.26$).

Results

We present results of all the three studies together and note the findings from each particular study with their conceptually similar measures assessing the same underlying constructs (for example, for parenting: parent report in study 1, observation in study 2 and youth report in study 3). The same pattern of findings across all the three studies with conceptually similar measures provides strong evidence for the robustness of the results.

Descriptive statistics. We first tested for potential gene–environment correlation between 5-HTTLPR and positive parenting. In none of the three studies did correlation analyses reveal significant rGE (study 1 (Alabama Parenting Questionnaire): $r=-0.06$, $P=0.30$;

study 2 (observed parenting): $r=0.01$, $P=0.75$; study 3 (EMBU-C): $r=-0.04$, $P=0.45$). Reported parenting was more positive for girls than for boys (study 1: $t(306)=2.29$, $P=0.02$; study 3: $t(1368)=4.10$, $P<0.001$), but there were no sex differences in observed parenting (study 2: $t(196)=1.52$, $P=0.13$). Sex differences in positive affect varied across the three studies as well. No sex difference in the positive affect ($t(306)=1.18$, $P=0.24$) was found in study 1; in study 2, girls reported higher levels of positive affect than the boys ($t(196)=2.14$, $P=0.03$); and in study 3, girls reported less positive affect ($t(1368)=-4.62$, $P<0.001$). Age did not have an effect on parenting and positive affect in any of the three studies. Ethnicity was not associated with parenting and positive affect in Studies 1 and 2, but showed a significant association with positive affect in study 3 ($F(1,1368)=10.96$, $P<0.001$). Given sex and ethnic differences found in (part of) the parenting and positive affect measures and potential concerns about population stratification, both sex and ethnicity were controlled for in analyses.

GxE analyses. The primary hypothesis that youths' 5-HTTLPR genotype would interact with parenting to predict youths' positive affect levels was tested with ordinary least squares regression analyses. The main effects of child genotype (5-HTTLPR) and the measures of positive parenting, as well as their interaction, were entered to predict youths' positive affect. In Studies 1 and 3, the effects of the L'S' and S'S' genotypes were tested against the effect of the L'L' genotype. In study 2, the effect of the S'S' genotype was tested against the effect of L' carriers, because L'L' genotype consisted of a too low number of participants ($N=39$) to be used as reference category. As shown in the Table 1, the interaction of 5-HTTLPR with positive parenting significantly predicted youths' positive affect in all the three studies. Neither gender nor ethnicity moderated this GxE.

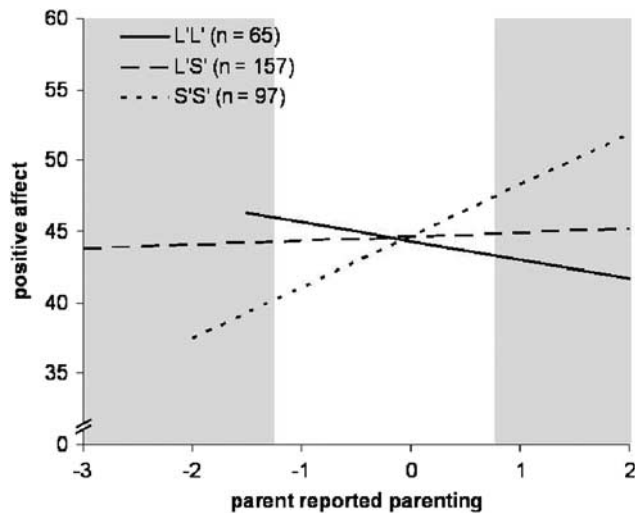
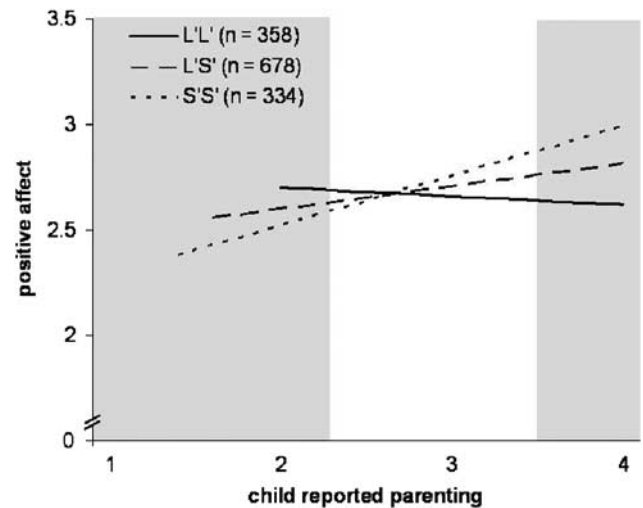
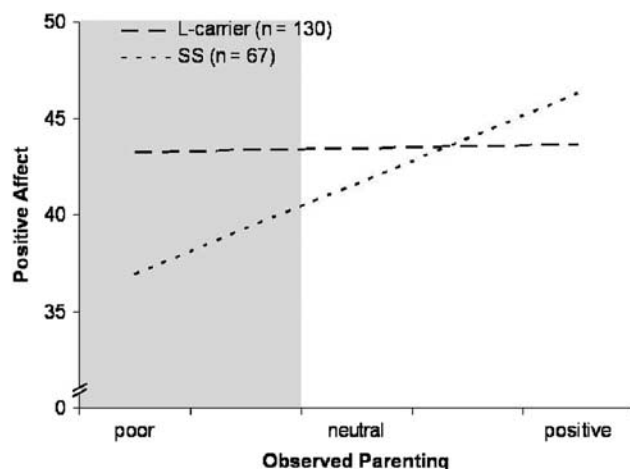
We estimated regions of significance⁵⁵ to further test the DSH hypotheses.⁵⁶ In study 1, positive affect differed significantly between the genotypes when positive parenting was lower than 1.23 s.d. or higher than 0.87 s.d. than the mean score on the Alabama Parenting Questionnaire (Figure 1). In study 2, positive affect differed significantly between the genotypes at the two least supporting levels of observed parenting (Figure 2). In study 3, positive affect differed significantly between the genotypes below 2.3 and above 3.5 points on the 1–4 EMBU warmth scale (Figure 3).

Discussion

The serotonin transporter promoter polymorphism, 5-HTTLPR, interacted with parenting behaviors to predict youths' level of positive affect. Consistent with our *a priori* hypothesis based on the DSH framework, the association between positive/supportive parenting and youths' positive affect varied as a function of youths' 5-HTTLPR genotype. Youth carrying two functional short copies of 5-HTTLPR exhibited significantly lower levels of positive affect in an environmental context of unsupportive parenting in all the three studies, and significantly higher levels of positive affect in positive, supportive parenting contexts in studies 1 and 3,

Table 1 5-HTTLPR genotype x positive parenting predicting youths' positive affect^a

	Study 1 (N = 307)			Study 2 (N = 197)			Study 3 (N = 1370)		
	B	s.e.	β	B	s.e.	β	B	s.e.	β
Constant	-0.03	0.16		-0.16	0.16		0.17	0.10	
Male sex	0.09	0.12	0.04	-0.26	0.14	0.13	0.26	0.05	0.13**
Ethnicity ^b	-0.05	0.13	-0.02	0.07	0.16	0.03	-0.30	0.09	-0.09**
Positive parenting ^c	-0.15	0.14	-0.15	0.01	0.09	0.01	-0.03	0.05	-0.03
5-HTTLPR L'S'	0.04	0.15	0.02				-0.08	0.06	-0.04
5-HTTLPR S'S'	0.04	0.17	0.02	-0.15	0.15	-0.07	0.05	0.08	0.02
L'S' X parenting	0.03	0.16	0.02				0.09	0.06	0.07
S'S' X parenting	0.41	0.17	0.22*	0.33	0.15	0.19*	0.20	0.08	0.09*

^aZ-score on the Positive And Negative Affect Scale for Children (PANAS-C; study 1 and 2) or Behavioral Activation System (BAS) drive (study 3).^bCaucasian ethnicity in studies 1 and 2, Dutch ancestry in study 3.^cZ-score on the Alabama Parenting Questionnaire (APQ; study 1), observed parenting (study 2) or child-reported My Memories of Upbringing for Children (EMBU) parental warmth (study 3) representing the effect of positive parenting in children with the 5-HTTLPR L'L' genotype (studies 1 and 3) or L' carriers (study 2).* $P < 0.05$ ** $P < 0.001$.**Figure 1** Interaction between 5-HTTLPR genotype and parent-reported positive parenting predicting youths' level of positive affect in study 1. The shaded areas represent regions of significance.**Figure 3** Interaction between 5-HTTLPR genotype and child-reported parental warmth predicting youths' level of positive affect in study 3. The shaded areas represent regions of significance.**Figure 2** Interaction between 5-HTTLPR genotype and observed parenting (ranging from lack of support/positivity to supportive/positive) predicting youths' level of positive affect in study 2. The shaded area represents the region of significance.

as indicated by the regions of significance. In contrast, youth carrying the L' allele of 5-HTTLPR (that is, L'S' and L'L' genotypes) showed relatively consistent levels of positive affect across both the supportive and unsupportive parenting environments. This pattern aligns with the DSH in that genetically susceptible individuals respond to their environment in a 'for better and worse' manner, in which outcomes are enhanced under enriched environments and are poorest under risk environments. Importantly, this GxE pattern was consistently found in three independent samples, in which both parenting behaviors and positive affect were assessed via varying methods that measured similar underlying constructs. As such, the GxE was conceptually reproduced and provides evidence of the robustness of this effect that cannot be easily explained away by the use of specific, particular methods or measures.

Aspects of DSH models have been examined in prior research, yet the vast majority has focused on the absence of negative environments and the lack of maladaptive outcomes.²⁵ A primary way in which this work advances

knowledge is expanding the study of genetic susceptibility among youth experiencing the full range of environmental contexts (from positive/supportive to negative/unsupportive parenting), and demonstrating that this GxE predicts both low–high levels of positive emotion. It is important to study youths' positive emotion because the full range, from low–high positive affect, is implicated in vulnerability to psychopathology and broad socio-emotional functioning.^{1–10}

Although considerable prior research shows that dysregulation of positive emotion systems and difficulties upregulating positive affect are implicated in psychopathology, scant research investigated both molecular genetic and environmental interactions contributing to the positive affect in youth. Our GxE results refine and potentially clarify prior, inconsistent main effect association studies that sought to demonstrate links between 5-HTTLPR and psychiatric disorder (for example, depression).⁵⁷ Our findings suggest that 5-HTTLPR may be a plasticity gene²⁵ that confers responsivity to environmental inputs. Previously equivocal GxE findings in depression,³⁶ focused on 5-HTTLPR as purely a risk gene in the context of negative environments, may have occurred because a differential susceptibility model may best capture the relationship between the environmental conditions and genetic risk in a 'for better and worse' manner. Likewise, prior research shows that negative/unsupportive parenting behavior is associated with risk to psychopathology¹⁶ and poor socio-emotional health.¹⁴ Our results suggest that these simple main effect associations can be refined, and prediction of psychopathology can be improved by joint consideration and co-action of genetic plasticity under negative environmental conditions.

Although S homozygotes with negative rearing experiences may be at heightened risk to psychopathology by virtue of low positive affect, our 'for better and worse' findings also highlight the plasticity of 5-HTTLPR as a susceptibility gene. Youth carrying two short alleles exhibited higher levels of positive affect when reared by positive/supportive caregivers. Various empirically supported parenting treatments and preventions have proven efficacious at reducing psychopathology by augmenting positive, supporting parenting practices.^{58,59} Findings from the present studies suggest that the main effect of parenting interventions may be significantly enhanced for genetically susceptible youth carrying plasticity genes, such as 5-HTTLPR. Likewise, some genetically susceptible youth who have experienced consistent positive/supportive parenting may be resilient and protected against developing psychopathology when faced with other negative environmental stressors, because such youth may be able to upregulate positive emotion to counteract deleterious consequences and negative emotion resulting from stressful events.^{60–62} In sum, and as highlighted by the DSH, susceptibility genes such as 5-HTTLPR may not bestow vulnerability to psychopathology *per se*, but instead confer enhanced reactivity and responsivity to environmental contexts, such as developmentally salient influences of parenting.⁶³

The present research had various strengths and limitations. An important strength is testing of the GxE effects in three independent studies with different ascertainment of parenting and positive affect. This suggests a robust GxE effect that

is not linked solely to one environmental assessment method. A second strength, as noted above, is the explicit focus on rigorously investigating DSH's conceptualization that genetically susceptible individuals are more responsive to environmental contexts 'for better and worse' by assessing the full range of both environment and outcome and not merely the lack of adversity or absence of negative outcomes.

On the other hand, one limitation includes investigation of a single plasticity gene, in contrast to several susceptibility genes (for example, DRD4)^{18,22} or a cumulative genetic plasticity index comprised of several genes.¹⁹ Although we purposefully selected 5-HTTLPR *a priori* as the susceptibility gene based on prior theoretical and empirical research,^{25,31,64,65} highlighting its likely function as a plasticity gene that is responsive to differing environmental contexts, future research would benefit from replicating these findings and extending them with other theoretically grounded plasticity genes. A second limitation is the use of correlational design rather than experimental manipulation of environmental context. Future research could investigate parenting interventions shown to enhance positive, supportive parenting⁵⁸ in the context of a genetically ascertained sample to investigate whether youth carrying plasticity genes respond with enhanced positive affect to supportive parenting. Last, putative mechanisms underlying the demonstrated GxE remain unknown and untested. One possible reason that youth carrying two short alleles of 5-HTTLPR are more susceptible to the full dimension of parenting is, genes involved in serotonergic system functioning are likely implicated in reward and punishment systems.^{18,25} Such youth may be more susceptible to both positive and negative parenting effects by virtue of being more responsive to parental rewards and punishment, respectively, and in turn, greater or lowered positive affect as a result.

In summary, findings from these three studies provide the first empirical evidence in youth, consistent with the DSH, that genetically susceptible individuals are more responsive to the full range of environmental contexts, and exhibit enhanced outcomes under positive/supportive contexts and poorer outcomes under negative environments. The association between positive/supportive parenting and youths' level of positive affect in children and adolescents was significant only among youth carrying two short alleles, but not those carrying a long allele, of 5-HTTLPR. Consequently, 5-HTTLPR may confer susceptibility to environmental context for positive affectivity among the youth.

Conflict of interest

The authors declare no conflict of interest.

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